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Serum bilirubin at 24 h of life birth as a predictor of significant hyperbilirubinemia in preterm neonates

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ABSTRACT

Background: As hyperbilirubinemia is one of the key contributors to brain damage and is crucial to identify those instances that are at risk as it is more prevalent and severe among the preterms. Many studies are available in the literature for terms babies but there is paucity of data for pre terms. **Aims and Objectives:** The aim of this study was to assess serum bilirubin at 24 h of live birth as a indicator of significant hyperbilirubinemia in preterm neonates. **Materials and Methods:** It was a prospective observational study conducted in the department of pediatrics of tertiary care center, Jodhpur on 150 preterms born within 33–36 weeks 6 days after considering the exclusion criteria in the study. Area under the receiver operating characteristic (ROC) curve was used to identify significant hyperbilirubinemia within 1 week of life, along with it the cutoff value of total serum bilirubin (TSB) at 24 h of life was calculated. **Results:** A total of 150 enrolled preterm newborns were followed up. TSB at 24 h of life was proved to be significant using the ROC curve, where area under the curve is 0.96 which was statistically significant. Among 150 preterms, 70 newborns with TSB >4.2 mg/dL developed jaundice, and 65 babies (98.48%) required phototherapy. Hence, preterms with TSB >4.2 mg/dL have a significant risk of developing hyperbilirubinemia. (Sensitivity: 98.48%, specificity: 94.05%, negative predictive value: 98.75%, and positive predictive value: 92.86%). **Conclusion:** TSB for preterms at 24 h of life can support to predict the significant hyperbilirubinemia successfully. Preterms with cutoff value of serum bilirubin level >4.2 mg/dL are observed to be more prone to develop significant hyperbilirubinemia requiring appropriate intervention at the earliest.

Key words: Hyperbilirubinemia; Serum bilirubin; Preterm neonates

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INTRODUCTION

Hyperbilirubinemia, or "jaundice," is yellowish-green skin and sclera pigmentation caused due to increase in bilirubin production or defects in the clearance.[1] Jaundice is commonly seen in the 1st week of life of neonates affecting 60% term and 80%.[2] Around 4% of term neonates are readmitted during their 1st week of life with jaundice in 85% cases.[3] A total serum bilirubin (TSB) >5 mg/dL, called neonatal hyperbilirubinemia, is commonly seen in neonatal wards. Significant hyperbilirubinemia (TSB >12.9 mg/dL) and excessive hyperbilirubinemia (TSB values above the 95th percentile on the hour-specific Bhutani Normogram) are seen in only 5–6% of the healthy newborn population.[4] Prematurity, birth trauma, blood group incompatibilities, medications (oxytocin, diazepam, erythromycin, and chloramphenicol), polycythemia, infrequent feeds, and delayed meconium passage are the common risk factors for hyperbilirubinemia in neonates.[5]

Bilirubin is a yellowish pigment formed in the liver by the breakdown of hemoglobin and after conjugation it is excreted in bile. Jaundice may be physiological or pathological based on the bilirubin levels in neonates.[6-8]

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Physiological jaundice occurs within 2–3 days of birth, with a increase in TSB levels to 6–8 mg/dL or up to a maximum of 12 mg/dL on 3rd day of life.[9] Under normal circumstances, the jaundice becomes visible on the 2nd and 3rd day (36–72 h) and peaking by the 4th day of life. In pathological jaundice, from the 1st day of birth the TSB levels start increasing beyond the normal values, that is, >5 mg/dL [on day 1]; 10 mg/dL [on the 2nd day] and thereafter 12–13 mg/dL to the pathological level of >17 mg/dL.[2,5]

The two important neurological manifestations of hyperbilirubinemia are acute bilirubin encephalopathy and kernicterus.[5] Neurological complications may be caused due to unmonitored and untreated hyperbilirubinemia, this compels to identify the hyperbilirubinemia and initiate appropriate treatment.[10] A follow-up visit after 2–3 days of hospital discharge of neonates is recommended by the American Academy of Pediatrics (AAP) to timely detect significant jaundice.[11] Jaundice assessment may be done clinically or through quantitative measurement. Visual inspection of jaundice is considered to be inaccurate, but it is reasonably accurate if done properly to note the severity of jaundice (Kramer's rule). The foundation of successful hyperbilirubinemia management has been the quantification of level of jaundice. Transcutaneous bilirubinometry (TCB),[12] conventional van den Bergh test-quantitative method,[13] and end-tidal carbon monoxide levels-index for the rate of bilirubin synthesis[14] are some of the quantitative measurement modalities. Among them, high-performance liquid chromatography[2] is the gold standard for measurement of TSB, which is performed by van den Bergh reaction. Serial TSB measurements (between 18 and 72 h of discharge) may be useful in predicting the risk of developing severe hyperbilirubinemia.[15] A guideline for the management of hyperbilirubinemia in new-born infants >35 weeks gestation has been published by the AAP.[16] However, the AAP has not published universal guidelines for preterm infants.

Bilirubin levels and the risk of developing hyperbilirubinemia have been associated, according to various reports, but there is a lack of literature on preterm infants as compared to term one. To identify preterm neonates at risk of developing substantial hyperbilirubinemia in the future, this study was conducted to evaluate the predictive value of serum bilirubin levels at 24 h postnatal age.

Aims and objectives

1. To predict the significant hyperbilirubinemia in preterm neonates by measuring total serum bilirubin at 24 hours of life.
2. To determine area under the ROC curve for 24 hours serum bilirubin for identifying significant hyperbilirubinemia within one week of life.

MATERIALS AND METHODS

This hospital-based prospective observational study was conducted in the department of pediatrics of tertiary care center, Jodhpur, Rajasthan, for the duration of 6 months from June 2022 to December 2022. Sample size was calculated using area under receiver operating characteristic (ROC) curve which was assumed 0.977 on the basis of previous studies.[9]

The following input values are chosen for the sample size calculation using the SciStat application.

1. Type-1-alpha error (significance) – 0.05
2. Type-2-beta error (1-power) – 0.20
3. Null hypothesis value – 0.5
4. Ratio of sample size in (negative/positive group) – 7.3.[9]

Where, the negative group defines the number of subjects with non-significant hyperbilirubinemia, and the positive group defines subjects with significant hyperbilirubinemia. The minimum sample size obtained was 25. To increase the feasibility of the center with 20% dropouts, the total sample size of 150 subjects was taken for the study.

All preterm neonates delivered in gestational age 33 weeks to 36 weeks 6 days in labor room/operation theatre in hospitals attached to the tertiary care center, Jodhpur, were recruited for the study. The study was conducted after ethical approval from the Institutional Committee (Ethical approval certificate reference number: SNMC/IEC/2022/Plan/631). All preterm babies satisfying the study criteria were enrolled after excluding Rhesus and ABO incompatibility, birth asphyxia, congenital malformation, maternal drug intake, etc. Before enrolment, the detailed procedure of the study was informed, and consent to participate from the parents/guardian was taken in their own vernacular language. On enrolment, their personal and demographic information involving name, age, sex, date of enrolment, birth order, weight with detailed maternal history, and gestational age assessment by the new Ballard scoring system is noted. The investigations were done in all enrolled preterm babies. The TSB level of all enrolled preterm babies was obtained at 24 h of life. As practically it was not feasible to obtain a sample exactly at the completion of 24 h of life, but we have tried to obtain value even at the earliest of 24 h ± 1 h. These enrolled babies were clinically followed up for the appearance of jaundice by performing TCB measurement up to 7 days, and those babies who develop jaundice, their subsequent serum bilirubin levels for every 24 h were obtained.

Following the NICE guidelines, babies with significant hyperbilirubinemia were given phototherapy as per their gestational age.[11] The observed baseline maternal and

neonatal characteristics are depicted in Table 1. A cutoff value was calculated at 24 h of life after statistical analysis of the obtained values and observations, which would predict the occurrence of significant hyperbilirubinemia.

RESULTS

During the 6-month study period, a total of 150 preterm babies fulfilling the inclusion criteria were enrolled and evaluated as per the study protocols.

We have observed in the study that, out of the 150 enrolled infants, 66 babies (44%) developed jaundice requiring phototherapy, and 84 babies (56%) did not, as shown in Table 2.

The 24 h serum bilirubin level was evaluated, predicting if these babies would develop significant jaundice in the 1st week of neonatal life. The cutoff value of TSB of 4.2 mg/dL was obtained, which had a sensitivity of 98.48% and a net present value (NPV) of 98.75 with an accuracy of 96%. It means that this cutoff value has a greater significance for the subsequent development of jaundice, as depicted in Table 3.

Occurrence of significant hyperbilirubinemia can be predicted for the healthy preterm of 33–36 weeks and 6 days of gestation age by using the hypothesis of TSB at 24 h of life under the ROC curve. Moreover, the area under the curve (AUC) was 0.96 and was statistically highly significant (Figure 1).

Table 1: Baseline characteristics

Characteristics	No. (%)
Maternal	
Type of delivery	
Normal vaginal delivery	96 (64)
Cesarean	54 (36)
Parity	
1	66 (44)
2	34 (22.66)
≥3	50 (33.33)
Blood group	
A	44 (29.33)
B	55 (36.66)
AB	29 (19.33)
O	22 (14.66)
Neonatal	
Sex	
Male	70 (46.67)
Female	80 (53.33)

Table 2: Babies requiring phototherapy

Jaundice requiring phototherapy	Number of cases	%
Yes	66	44.00
No	84	56.00
Total	150	100

DISCUSSION

Hyperbilirubinemia is a commonly encountered problem in neonates in the 1st week of life, affecting around 80% of preterms.[2] Hence, we planned to study the serum bilirubin level at 24 h of life birth as a predictor of significant hyperbilirubinemia in preterm neonates.

On the basis of statistical analysis, it was observed that the babies having TSB in the range of 4–5 mg/dL were found to have greater risk of development of significant jaundice. The cutoff value of 4.2 mg/dL at 24 h of life was obtained by plotting the ROC curve. The results show that the test has a 96% accuracy, specificity 94.05% and positive predictive value of 92.86%, and NPV of 98.75%. This indicates that if babies of 33–36 weeks and 6 days of gestation age at 24 h of life have a TSB level of >4.2 mg/dL show a high risk of developing subsequent hyperbilirubinemia and subsequently requiring phototherapy. Similar significance is also proved in earlier studies done on preterms.[17,18]

As per the study by Awasthi and Rehman[19] in 1998, the subsequent phototherapy requirement was there at a cutoff value of TSB of 3.99 mg/dL having a sensitivity of 64.2%. This study had its limitations as the ROC analysis was not used to determine the cutoff value and the mean serum bilirubin at 18–24 h was used for the prediction test.

Table 3: Results for a cutoff TSB value of 4.2 mg/dL at 24 h of life

TSB at 24 h (mg/dL)	With hyperbilirubinemia		Without hyperbilirubinemia		Total	
	n	%	n	%	n	%
>4.2	65	98.48	5	5.95	70	46.6
≤4.2	1	1.52	79	94.05	80	53.3
Total	66	100	84	100	100	100

TSB: Total serum bilirubin

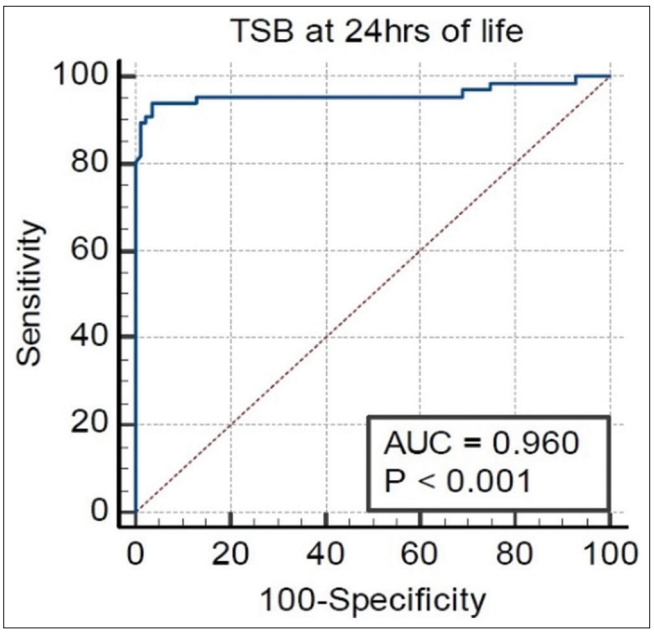

Figure 1: Receiver operating characteristic curve

In our study, on the basis of using the ROC curve, at 24 h of life the cutoff value of 4.2 mg/dL was determined for the occurrence of significant hyperbilirubinemia in the 1st week of life. The AUC of the ROC curve (Figure 1) was 0.96 with a P<0.001 and both are highly significant for the given value. Similar to it, the ROC curve is utilized in various Indian studies, such as conducted by Randev and Grover[20] in 2003 at Shimla on 228 full-term neonates in which using ROC curve analysis, a bilirubin value of 6.4 mg/dL within 24 h of life was determined to have the significant predictive value for subsequent hyperbilirubinemia with a specificity of 80.11% and sensitivity of 87.5%.

Limitations of the study

1. In this study, the sample size is small and heterogeneous, that comprises of different gestational ages and birth weights, as it affects the quality of result.
2. The infants were followed upto 7h day of life only, and it i is possible that some of these babies might have developed late jaundice and were missed.
3. The infants were evaluated clinically for progression of jaundice and subsequent level of bilirubin depended upon the TCB values, which is unreliable in infants less than 35 weeks of gestation age.

CONCLUSION

Preterm neonates are at high risk and vulnerable to bilirubin-induced neuronal dysfunction, so they require early intervention. Many studies have been conducted on term neonates to predict the subsequent hyperbilirubinemia, but not on preterm infants. Our research has, therefore, given us a better understanding of the value of routine TSB screening on the 1st day of life, which, if implemented at the appropriate time, will undoubtedly aid in identifying preterms, at risk for hyperbilirubinemia and prevents complications related to jaundice.

However, further studies with larger sample sizes will help establish standard consensus guidelines in this regard. On the basis of our study, we recommend the screening of all preterms of gestational age 33–36 weeks and 6 days by TSB level before discharge from the hospital at 24 h of life to prevent complications related to hyperbilirubinemia.

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TC- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, and data analysis; **HKM-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision and submission of article; **SM-** Design of study, statistical analysis and interpretation, editing, and manuscript preparation and revision; **MP-** Review manuscript, preparation of master chart, tables, analysis and coordination; **RK-** Review manuscript, preparation of master charts, tables, and graphs; **MM-** Manuscript revision and critical appraisal and analysis; **MKG-** coordination, Literature survey, graphs and tables and manuscript revision**; PC-** Review and master charts.

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